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Review Article

MULTI DRUG RESISTANCE IN CANCER THERAPY-AN OVERVIEW

HARISH KADKOL[1], VIKAS JAIN[1], AMIT B PATIL[1*]

[1]Department of Pharmaceutics, JSS College of Pharmacy, JSS Academy of Higher Education and Research, Mysuru 570015, India
Email: amitbpatil@jssuni.edu.in

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ABSTRACT

Multidrug resistance is a mechanism by which chemotherapeutic drugs develops resistance in cancer treatment. Multidrug resistance (MDR) is the most essential test to compelling chemotherapeutic efficacy against tumor growth. Improvements in the DNA microarray, proteomics innovation and the outgrowth of focused treatments convey the new ways to deal with the drug resistance in spite the structures of the new chemotherapy drugs. The chemotherapeutic drugs develops multi drug resistance as the drug treats the tumor but the cells tends to shows a resistant effect for the same drug when used again, despite their diverse concoction structure and distinctive mechanism of intracellular activity. The scope of the review explains us about multi drug resistance, the mechanisms of malignant growth inhibiting drugs and overcoming multidrug-resistance.

Search Criteria: A literature survey was done in Scopus, PubMed, Google Scholar, and Science Direct database for articles for published articles from 1946 to 2019 on multidrug resistant and its mechanism on cancer.

Keywords: Multidrug resistance, Cancer, Chemotherapy, Chemo sensitizer

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INTRODUCTION

Multidrug Resistance (MDR) in cancer cells is a critical hindrance towards accomplishment of chemotherapy in numerous malignancies. Multidrug resistance is a phenomenon whereby tumor cells *in vitro* have been presented to one cytotoxic drug creates cross-protection from a scope of fundamentally and practically random mixes. The drug resistance that creates in tumor cells regularly results from raised articulation of specific proteins, for example, cell-membrane transporters, which can result in an expanded efflux of the cytotoxic drugs from the cancer cells, hence bringing down their intracellular activity [1, 2]. In addition, MDR happens characteristically in tumor without past introduction to chemotherapy drugs [3]. In addition to, normal disease medicines, for example, medical procedure, radiation treatment, chemotherapy, mix treatment and laser treatment; the specific treatments depend on the better origination of the science and sub-atomic hereditary qualities in tumor movement utilized for the favourable actions [4]. Currently, regardless of these developments, the likely alternative for malignant growth treatment is chemotherapy. At present, 90% of failure in chemotherapy are amid the attack as well as metastasis of tumor identified with drug obstruction. In chemotherapy, by subsequent the organization of a specific drug, countless tumor cells wind up impervious to the drug. Along these lines, the drug resistance shows up as a significant issue in the field of cancer [5]. Tumor formed from tissues, requires high articulation of transporter proteins show characteristic multidrug resistance from cytostatic even before chemotherapy is started. The MDR in tumor got from different tissues shows up endless supply of qualities coding for transporter proteins by a cytostatic moiety coming about into gaining MDR over the span of the treatment. Past findings of about 35 y have hurled different theory identified with the components of MDR improvement and furthermore the modulators tailored to address this issue. The novel tumor growth medicines concentrate on oncogenes, tumor inhibiting qualities and RNA impedance (RNAi) are extended [6]. The rationales behind the approach are, a) the kinases restraint is associated with, cell expansion, b) enhancing the fast-safe reactions in malignant growth, c) specifying the drugs, d) drug conveyance in malignant growth cells and e) diminishing the reactions of anticancer drugs, etc. [7]

Multi-drug resistance (MDR) in the cancer chemotherapy has been called attention to as the capacity of cancer cells to get by against an extensive variety of anti-cancer drugs [8]. MDR mechanism might be produced by expanded administration of the drug outside the cells. So, the drug retention is decreased in these cells that change in size, structure and site of activity in the cell [9]. For instance, a typical anticancer drug adriamycin, acts in the nucleus of a drug-sensitive cell meddling with the transcription of DNA and its synthesis during cell division.

Another conceivable method to crush multidrug-resistant tumor cells might be to exploit the plain certainty that they contain P-glycoprotein. Monoclonal antibodies bearing a radioactive compound or a toxic drug could be focused to P-glycoprotein with the end to kill tumor cells that are untreatable by conventional means (fig. 1) [10].

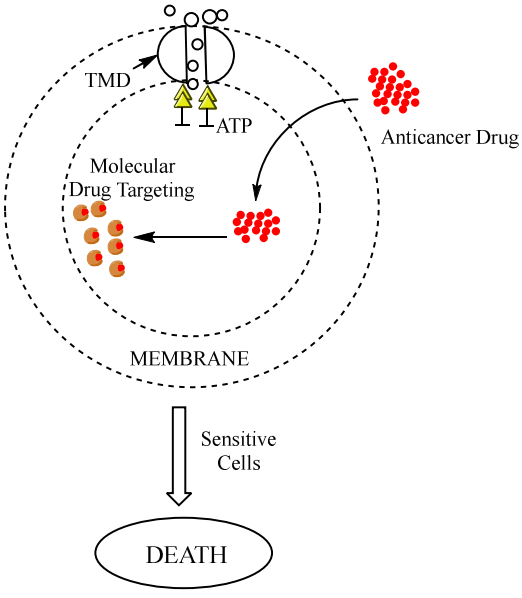

Fig. 1: Diagram of anticancer drug access into a cancer cell through the membrane

Mechanisms of multidrug resistance

Various mechanisms have been proposed to intervene multidrug resistance in malignant growth cells. Such components can be ordered as non-cell or cell dependent on the elements adding to MDR development (fig. 2) [11].

This mechanism typically related to specific sorts of diseases which demonstrate intrinsic or common protection from chemotherapy at the underlying of the drug. Change to the cancerous state requires the cells to develop beyond their normal limits and such a procedure ought to be helped by a very much organized vasculature. In any case, in certain strong tumor angiogenesis is endangered [12]. Prompting poor vasculatures that obstruct the action of the drug to the tumor cells in a way that restricts the drug-initiated cytotoxicity. The development condition in which tumor cells multiply is especially not quite the same as that of the typical cells. Absence of sustenance and hypoxia because of poor vasculature and the resultant lactic acid aggregation could give protection from tumor cells against drugs that follow up on effectively separating cells or the cell take up of which requires a pH angle [13].

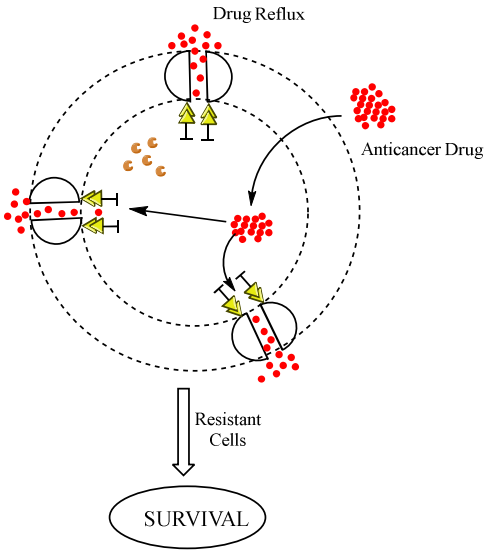

Fig. 2: Schematic presentation of the phenomenon of MDR in cancer cells non cellular MDR mechanism

Cellular MDR mechanism

Cell MDR mechanisms might be delegated non-traditional/non transport based or established transport-based mechanisms. Non-transport-based cell MDR mechanism include compound frameworks that limit the coveted action of the drug without adjusting its successful fixation inside the cell [14]. Glutathione-S-transferase (GST) an essential catalyst of xenobiotic digestion catalyzes the biotransformation of natural atoms by conjugating them with polar particles to encourage their discharge [14]. GST is known to intervene biotransformation of different anticancer drugs and its hoisted dimension has been accounted for in different resistant cancer cell lines [15].

The transport based established cell mechanism of MDR includes the efflux of drug from the cell by different energy dependant transport proteins, and in this manner restricting it from coming inside the cell [16]. ATP-binding tape (ABC) transporters are a group of proteins that intervene MDR through ATP-subordinate drug efflux pumps [17]. Overexpression of ATP-restricting tape (ABC) transporters has been appeared to be in charge of MDR. Various transporter proteins of the ABC superfamily has been described and incorporate P-glycoprotein, multidrug resistant related protein-1 (MRP1), its homologs MRP2-6 and the bosom tumor obstruction protein (BCRP) [18-20].

An earlier removing of a drug aggregation by the cells might affect together from reduction of drug influx and increment of drug efflux from the cells. Since most chemotherapeutic drugs enters cells by dispersion through the plasma membrane, cell changes in drug inundation can be associated with changes in the cell layer structure. Both electron microscopy and examination of the lipids of the layers of MDR cells to be uncovered contrasts between some drug delicate and drug resistance cells [21].

Drug efflux from cancer cells

It came as something of an unexpected that the real component of multidrug resistance in refined malignant growth cells was the declaration of a vitality subordinate drug efflux pump, referred to on the other hand as P-glycoprotein (P-gp) or the multidrug transporter [22, 23]. This efflux pump, the result of the MDR1 gene in the human [24] and the result of two diverse related qualities, mdr1a and mdr1b in the mouse [25, 26], was one of the primary individuals portrayed of an expansive group of ATP-subordinate transporters known as the ATP-restricting tape (ABC) family [27]. This efflux mechanism assumes a vital job in counteracting over cluster of toxins inside the cell [28]. As anyone might expect, ABC transporters are profoundly communicated in the epithelium of the liver and digestive tract, where the proteins secure the body by pumping drugs and other hurtful atoms into the bile pipe and intestinal lumen. They likewise assume a huge job in the keeping up the blood-brain barrier [29, 30]. Natural-product drugs incorporate huge numbers of the usually natural-product anticancer drugs, for example doxorubicin, daunorubicin, vinblastine, vincristine, taxol and additionally numerous ordinarily utilized pharmaceuticals varying from anti-arrhythmics and antihistamines to cholesterol-bringing lowering statins [31] and HIV protease inhibitors [32].

Reducing the absorption of the drugs

The ingestion of the anticancer operator into the tumor cells can happen by uninvolved exchange (e. g. doxorubicin and vinblastine), encourage dispersion and enact the vehicle (for instance, nucleoside analogues) [34]. The cytotoxic specialists can enter the cells by means of bearing of the concentration gradient by the three ABC transporter atoms which were referenced previously. Be that as it may, the retention of the drug in the cells by means of course of a high fixation slope happens just through dynamic transport [35]. Most of the layers transporters have a place with solute bearer SLC transporters (transports minerals, nutrients and so forth). Lessening the assimilation of the drugs can happen at two fundamental ways: 1) diminishing the tendency to drugs binding and additionally and 2) Decreasing the quantities of transporters. A portion of the specialists utilize the explicit transporters to enter the cells [36]. Mutations in these transporters hinder them and decrease the ingestion of the drugs. The protection from Methotrexate is happened normally by the human folate bearer's (HRFC) quality change in the patients with intense lymphoblastic leukaemia. The transformation of G point at nucleotide 133 and the substitution of lysine by glutamic corrosive in the first transmembrane space of HRFC protein decreases the propensity of the drugs to tie the transporter [37].

Drug inactivation

Components that inactivate drugs can lessen the measure of free drug accessible to tie to its intracellular target. Over 80% of the anti-metabolite 5-fluorouracil (5-FU) is regularly catabolized by dihydropyrimidine dehydrogenase (DPD), primarily in the liver [38]. In vitro studies have shown that DPD overexpression in tumor cell lines presents protection from 5-FU [39]. Moreover, abnormal amounts of DPD mRNA articulation in colorectal tumor have been appeared to connect with protection from 5-FU [40, 41], apparently reflecting more prominent DPD-intervened debasement of 5-FU in these tumor [42]. Another imperative case of drug initiation and inactivation is seen in the GST superfamily, GSTs aid the improvement of drug obstruction through direct detoxification and by restraining the mitogen-enacted protein kinase (MAPK) pathway [43]. Height of GST articulation in tumor cells upgrades detoxification of the anticancer drugs, which results in less proficient cytotoxic harm of the cells [44]. This expansion is likewise connected with resistance from apoptosis started by a variety of stimuli [45].

Anti-folate drugs, for example, mitothrexate is polyglutamated by folylpolyglutamate synthase (FPGS), which expands their cell maintenance and substrate-binding affinity [46]. Diminished polyglutamation has been seen as a resistance mechanism to anti folates [47, 48].

Drug resistance due to reduced uptake of drugs

The retention of the anticancer specialist into the tumor cells can happen by passive exchange (e. g. doxorubicin and vinblastine), encourage dispersion and enact the vehicle (for instance, nucleoside analogs) [49] the cytotoxic agents can enter the cells by means of course of the focus inclination by the three ABC transporter particles which were referenced previously. Be that as it may, the ingestion of the drug into the cells by means of course of a high fixation slope happens just through dynamic transport [50]. Not very many drugs enter cells by endocytosis. In any case, a portion of the more up to date anticancer specialists, for example, immunotoxins that bind to cell surface receptors, can't slaughter cells except if they are internalized [51]. They are for the most part internalized through receptor interceded endocytosis. Malignant growth cell freaks that have flawed endocytosis are impervious to the two toxins and immunotoxins [52]. The vast majority of the membrane transporters have a place with solute bearer SLC transporters [transports minerals, nutrients and so forth]. Decreasing the absorption of the drugs can happen at two principle ways: 1. diminishing the inclination to drugs authoritative as well as 2. Decreasing the quantities of transporters. A portion of the specialists utilize the explicit transporters to enter the cells [53]. Cisplatin is usually used to treat cancers, for example, head and neck disease, testicular malignant growth, ovarian disease, and other strong tumor. It isn't know with sureness how cisplatin, a water-solvent compound, enters cells [54].

Enhanced DNA repair

Activity of DNA based proteins is to expel cisplatin-DNA byproducts and fix cisplatin induced sores. This makes the cell resistant to cisplatin-DNA. Atomic protein called XPE-BF (xeroderma pigmentosum group E restricting variable) were found to improve the cisplatin resistance. Removal of cross supplementing protein (ERCCI) is another method to fix the cisplatin damage. The size of the cross-supplementing protein increasing as there is a resistance of Carboplatin in tumor cells [54]. In cisplatin safe cells, there is a cross protection of carboplatin but is less as compared oxaliplatin or tetraplatin. Thus, there is scope of second line treatment. Interference of seminomatous germ cell like had 1.7 to 2.2 overlay in oppose to oxaliplatin with 3.9 to 6.1 overlay with cisplatin [55].

Alterations in target molecules

A treatment used for time span can be less effective or may no longer be useful in treating tumor. A basic case of estrogen based drug, for example tamoxifen may show reduced effect in malignancy. Patients will show change to an endocrine safe responsive state, where he would no longer show effect to tamoxifen treatment due to loss of estrogen receptor in tumor cells. This can be overcomed by estrogen aromatase inhibitor. This condition is trailed by complete lethargy to any endocrine control. Thus, it leads to obstruction or being unreactive to estrogen targets. Gene mutation is a normal process in cancer cells that give it the desired properties. Cytotoxic medications are said to disturb the cell survival [56].

Cancer cell heterogeneity

Notwithstanding the advancement drug resistance in cancer progenitor cells and grown-up disease cells by the instruments recently talked about, another part of disease backslide is the improvement of medication safe disease cells effectively present in the heterogeneous disease cell populace. Late examinations demonstrate that few cells inside this heterogeneous populace have immature microorganism properties and are normally medicated safe. An ongoing report on intense myeloid leukemia decided two existing together overwhelming clones. One was medicating touchy and the other medication safe. It is conceivable that re-event of this illness in patients after effective treatment might be the aftereffect of disease cell development from the medication safe clone [57]. This possibility exists in all types of disease, as all tumor are heterogeneous, because of distorted DNA fix components and cell demise pathway dysregulation. A clonal organization investigation of bosom malignant growth uncovered that bosom diseases may have monogenomic or different genomic tumor. Polygenomic tumor contain a wide range of kinds of clonal subpopulations, all of which may have distinctive medication sensitivities and resistance attributes [58].

Role of epigenetics in cancer drug resistance

A critical arrangement of systems that reason resistance from cancer treatment and that have not been promptly talked about are epigenetic adjustments, which can likewise impact carcinogenesis. The two fundamental kinds of epigenetic changes are DNA methylation and histone adjustment through acetylation or methylation. DNA methylation comprises methyl bunches official to cytosines at CG-dinucleotides inside locales known as CpG islands, basically found in upstream quality advertiser districts. In any case, methylation can happen at other loci all through the genome.

On the other hand, histone changes modify chromatin adaptation. For instance, histone acetylation opens the chromatin, while deacetylation closes it. These mechanisms at last manage the declaration of qualities all through the chromosome, and in malignant growth, this ordinary guideline is broken. For instance, tumor silencer qualities are regularly quieted by means of hypermethylation, and oncogenes are over-communicated by means of hypomethylation. In any case, epigenetic systems are normally reversible, and researchers take an advantage to develop treatment that counteract cancer resistance Later examinations recommend that epigenetic adjustments, for example, histone methylation and acetylation, may assume a role in the advancement of drug resistance. One investigation recommended that hypermethylation of the MDR1 advertiser is related with transcriptional constraint and chromatin basic changes [59]. Others have likewise proposed that DNA methylation is related with obtained multidrug obstruction. In investigations developing this thought, demethylation of the MDR1 advertiser in disease cell line was observed to be emphatically connected with the procurement of a multidrug safe phenotype [60].

Types of resistance

There is a distinction in the reaction between different tumor types. Tumor, for example, pancreatic disease has a constrained survival [61], in all probability because of a blend of disappointments, for example, to medical procedure and the consequent adjuvant chemotherapy, comprising either a gemcitabine-based treatment or a 5-fluorouracil based mix, for example, FOLFIRINOX [62]. In spite of the fact that the last treatment is more compelling, this is at the expense of genuine poisonous quality. Henceforth, pancreatic malignant growth is a sickness for which resistance is characteristic. Conversely, the greater part of bosom disease patients will be restored, because of a mix of viable screening, enhanced medical procedure and radiation, and powerful adjuvant therapy [63]. Indeed, even triple negative patients have a>70% 5-year survival. In this sickness and in stage III and IV patients gained obstruction is a noteworthy issue. For a subpopulation of bosom tumor patients, explicit foundations for resistance, for example, BRCA has been recognized, and luckily, for a subgroup of patient's viable new treatments are accessible.

Novel approaches to overcome multi drug resistance in cancer

Multidrug resistance (MDR) is the mechanism by which numerous malignant growths create protection from chemotherapy drugs, bringing about insignificant cell demise and the development of drug safe tumor. Nanoparticles that all the while convey chemotherapy drugs to tumor and restrain the MDR proteins that pump the remedial drugs out of the cell [64, 65]. The procedure is known as chemo sensitization, as obstructing this resistance renders the tumor exceedingly touches to the malignant growth slaughtering chemotherapy. MDR is a main consideration in the disappointment of numerous chemotherapy drugs. The issue influences the treatment of an extensive variety of blood malignancies and strong tumor, including ovarian, lung, and colon diseases.

Curcumin MDR block that works against doxorubicin MDR

Underneath Diagram showing the arrival of the active substance of the curcumin MDR nanoparticle inside a tumor cell. The blue stars represent to the curcumin that represses the MDR pumps situated in the cell layer [65]. Pumps hindrance permits the doxorubicin (orange circles) to stay in the cell at a high focus and enter the core (dim circle) where it acts to disturb cell division and kill the cell (fig. 3).

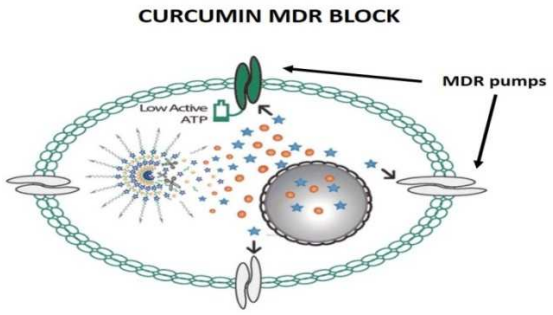

Fig. 3: Curcumin MDR block

Two distinct nanoparticle that test distinctive mechanisms for accomplishing chemo sensitization of tumor cells. The primary targets MDR breast cancer growth. The built round nanoparticle is made of a few layers. The focal point of the molecule is stacked with the anti-cancer drug doxorubicin [65]. The drug is encompassed by a water-repulsing (hydrophobic) container to shield it from the watery condition when the molecule is infused into the circulatory arrangement of a test creature or individual with tumor.

Once inside the breast cancer cell, a fourth part called curcumin which is intertwined with the doxorubicin focus is discharged alongside the doxorubicin. The curcumin is the part that blocks the cell apparatus that would pump the doxorubicin out of the cell [66-68]. Without the capacity to pump out the drug, the cell is presented to high grouping of doxorubicin, which kills the breast cancer cells (fig. 4).

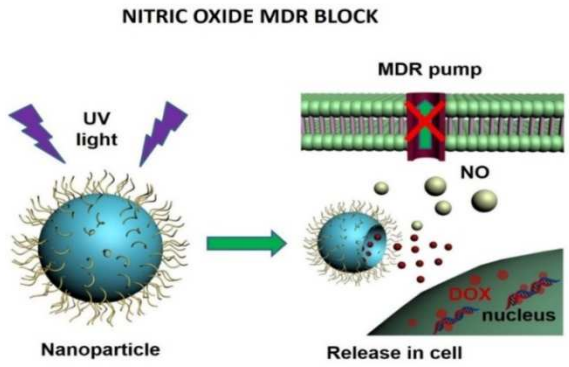

Fig. 4: Graphical representation of the UV-actuated MDR nanoparticle ruptures to discharge nitric oxide. (NO, green circles) that obstructs the MDR pump permitting doxorubicin (DOX, orange circles) to move in the nucleus, upset cell division, and execute the cell

MDR inhibitors that escape ABC transporters

There are numerous investigations to defeat MDR by hindering MDR transporters to stifle or evade MDR components. The utilization of anticancer medications that could escape from the ABC transporters may be an answer for maintain a strategic distance from medication resistance. Anticancer medications which are not the substrates of ABC transporters are alkylating drugs (cyclophosphamide), antimetabolites (5-fluorouracil), and the anthracycline adjusted medications (annamycin and doxorubicin-peptide). Another strategy to defeat protection from anticancer medications is to manage intensifies that would not be lethal themselves, however would repress ABC transporters [69, 70]. The aggravates that would invert resistance against anticancer medications are called MDR inhibitors, MDR modulators, MDR inversion operators or chemosensitizers. They may adjust more than one transporter. Clinical preliminaries disentangled the issues related with blend chemotherapy of anticancer drug(s) together with a MDR inhibitor. The primary factor to be resolved before leaving a clinical preliminary is to recognize the ABC transporter protein associated with medication resistance and to use an anticancer medication that would profit by restraint of that transporter protein. The anticancer drug[s] used should coordinate the transporter protein being hindered. Second factor is to screen the plasma focuses and *in vivo* viability of the tried MDR inhibitor to check that a successful inhibitory fixation was in actuality accomplished *in vivo*. The pharmacokinetic association between the anticancer drug(s) and the MDR inhibitor must be looked and stayed away from to keep a decrease in anticancer drug dosage.

MDR modulators that are specific to the P-Glycoprotein

Preventing P glycoprotein has taken a broad research since past 2 decades [71]. Special compounds like calcium channel blockers (e. g. verapamil), calmodulin enemies, steroidal specialists, protein kinase C inhibitors, immunosuppressive medications (e. g., cyclosporine, anti-toxins (e. g., erythromycin), antimalarial (e. g. quinine), psychotropic phenothiazines and indole alkaloids have been identified for protection against MDR [72, 73]. MDR associated first generation drugs didn't show activity for ABC transporters and there was a necessity for the drug to be given in high doses which ultimately gave rise to unsatisfactotory high poisonous effect [74]. Clinical preliminaries with original MDR drugs fizzled for different reasons, frequently because of reactions [75-76]. Number of original chemosensitizers were acted as a substrate for ABC transporters and showed a cytotoxic medication efflux. Adequate intracellular regulation was adopted due to high serum concentration of the chemosensitizer [76]. Recently developed chemosensitizers are progressively intense, less toxic, and specific for the P glycoprotein and other ABC transporter [77].

Use of antisense oligonucleotide, inhibits the P-Glycoprotein. Thus, antisense protein are widely been studied for the suppression of MDR by bypassing the P glycoprotein. Drugs like Idarubicin and Annamycin are poor substrates of MDR transporter, also bypasses P Glycoprotein as they are not transported by P Glycoprotein. Drugs showing rapid uptake kinetics, can bypass the P Glycoprotein such as Olivacine derivatives.

The first generation P gp modulators include cyclosporin, verapamil, tamoxifen, etc. They must be present in high concentration, to show the inhibitory effect. Second generation P gp such as valspodar and Biricodar are the substrate to Cyp P450 3A4 and the substrates of Pgp. Valspodar inhibits the metabolism of paclitaxel by Cytochrome P450 3A4. Thus, increases concentration of the drug. Similarly, Biricodar increases the concentration of paclitaxel by decreasing its clearance from the body. Third generation inhibitors of Pgp are currently oin clinical development such as Tariquidar, Diketopiperazine derivative and Cyclo-propyl-di-benzosuberane.

These third-generation inhibitors of Pgp bind with high affinity to the transporter pump but are not substrate to themselves. They induce a conformational change in the protein, thereby preventing transport of cytotoxic agent outside the cell. This ultimately increases concentration of cytotoxic drugs inside the cells [78, 79].

Usage of MDR inhibiting protein gene

MDR protein gene growth in the tumor occurs due to usage of anti-cancerous drugs. This articulation can be halted by the use of therapeutic inhibitors that influence the inhibitory pathway. For example, Protein like MDR 1 and cytochrome p450 (CYP3A4) was interfered with Taxol by its initiation of atomic steroid and xenobiotic receptor that quickly expanded medication effects.

ABCG2 protein is a perfect contender for human stem cell protection and for use as a selectable marker in gene therapy. But, R482G, a variant of ABC G2 holds advantages as it is a distinctive substrate as compared to the wild type protein [74]. Chemotherapy can be improved and accepted by the utilisation of an apoptosis initiating monoclonal agent that works against the CD20 receptor.

Circumventing MDR mechanism

Use of antiangiogenic drugs that target the epithelial cells instead of the tumor cells, can work on the MDR as well as non MDR tumor, for example drug thalidomide. A study showed that when irradicated myeloma was treated with autolougous tumor cell vaccine, it produces a strong cytotoxic effect that lead to graph rejection.

CONCLUSION

Multiple drug resistance in cancer is due to the cells being resistant to the drugs administered in chemotherapeutics. This leads to decrease therapeutically effect of the drug and proliferation of tumor. Various techniques are developed to overcome this effect and there is an ongoing research to overcome MDR. Chemo sensitizer are often used to reverse the effect of MDR and improve drug efficacy in tumor cells. It allows the drug to remain in the cell for a longer period improving treatment regime. Thus, in chemo sensitizing technique one drug would improve the action of the other chemotherapeutic agent. Other techniques include use of nanoparticles or nanomedicines up to the size of 400 nm that can overcome the MDR effect. Modulating reactive oxidative species in treating MDR is developing a wise scope in the treatment of chemotherapy. Thus, MDR must be overcome for better efficacy and improved results in cancer treatment.

ABBREVIATIONS

Multidrug resistance (MDR), Glutathione-S-transferase (GST), ATP-binding tape (ABC), multidrug resistant related protein-1 (MRP1), bosom tumor obstruction protein (BCRP), P-glycoprotein (P-gp), 5-fluorouracil (5-FU), dihydropyrimidine dehydrogenase (DPD).

AUTHORS CONTRIBUTIONS

All the author have contributed equally

CONFLICT OF INTERESTS

Author(S) declares no conflict of interest

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